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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,487	02/14/2001	Tito Andrew Serafini	10239-010	7095

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/783,487	SERAFINI, TITO ANDREW	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 32-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 32-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 23, 2004 has been entered.

DETAILED ACTION

This is an original application, filed February 14, 2001.

As indicated in the request for continued examination the after final amendment filed March 24, 2004, has been entered. Claims 28-31 and 61-158 have been canceled. Claims 1, 7, 32, 38 have been amended. Claims 1-27 and 32-60 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 32-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". The amendment of "wherein said first sequences are not expressed in said transgenic prior to the animals being made transgenic" is considered new matter. Applicants have pointed to page 60, lines 11-13, for support of the amendment. Review of the specification indicates "that the system gene product…is not present" and fails to teach anything about expression as presently recited in the claims. Moreover, the claim as amended appears to be redundant or confusing even in light of the specification because a transgene could not have been expressed prior to the making of the transgenic animal because the transgenic animal did not exist and the transgene was not present in the transgenic. Finally, the portion of the specification relied upon by Applicants does not teach about the particulars of the first sequence (as amended) rather the system as a whole used to generate the transgenic animal.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-27 and 32-60 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue

arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the invention is fully enabled and that the artisan can provide larger pieces of a promoter for example in the context of a BAC vector, noting specific results in newly supplied references (see attached Appendix). This is not found persuasive because review of the teachings of supplied references support the basis of the rejection. While the size of the promoter may matter to some extent in particular casess, Giraldo et al. teaches that copy number (page 86) also matters With the use of a YAC, there is an inherent problem with stability and thus the presence in stable lines (page 91). The results of Cavelier et al demonstrate that expression from a BAC clones can vary and is different in tissues assayed, some demonstrating

higher expression levels and some lower or non-detectable levels (see figure 2). Rui et al. teach that using the same construct expression differend among several independnet lines (page H1406). The teachings of the references provide further support for the need of more detailed guidance, and not a simple approach that larger sequences will remedy the art recognized limitations for the use of heterologous promoters in transgenes to practice the claimed method. In addition, the teachings further support the basis of the 35 USC 112, second paragraph, rejection in light of the varied expression levels one can obtain even with the same construct in separate independent lines. Examiner acknolwedges that even prior to the filing date of the instant application that many transgenic animals comprising large promoter sequences have been constructed (for example as outlined by Giraldo et al. (see Table 1), however the present specification provides no further guidance than presented in these prior art documents for making the claimed invention. With respect to genes associated with specific disorders, Applciants argue that these are readily known in the art and point ot Pamboz et al. and Schmauss et al. as supporting evidence. Applicants arguments are not found persuasive because again these reference further support the basis of the rejection. In this case, Schmauss et al. teach that dipamine D3 receptor expression is decreased in patients with schizophrenia, however knock-out mice that have no expression of the dopamine D3 receptor are phenotypically normal (page 14476), other genes change expression to compensate for the alteration, and there is not a clear coorelation with schizophrenic behavior in the KO mice and is 'paradoxical' to phenotypes predicted from humans (page 14480). The methodology of generating transgenics is relatively straightforward and simple to the skilled artisan, however the consequence of inserting and exprssing a gene and the resulting phenotype is sitill unpredictable and impirical. The present

specification provides an outline to make a product however fails to provide the necessary guidance to overcome art accepted limitations.

Again, as stated previously the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, Examiner acknowledges and agrees that "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation." However, " The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Examiner agrees with the summary of the basis of the rejection set forth by Applicants and notes that in response to each of the specific basis of the rejection Applicants argue and rely on the skilled artisan for optimizing sequences to obtain and practice the claimed method. These arguments are not found persuasive because each specific basis of the rejection is an art recognized limitation. Examiner has provided sound scientific reasoning and specific scientific references supporting the basis of the rejection, thus providing a *prima facie* case. The particular teachings in the specification are noted, however none of the general guidance provides the necessary guidance to overcome art recognized limitations set forth in the basis of the rejection. Applicants' arguments do not contest the art recognized limitations set forth in the basis of the rejection, rather the traverse of the rejection focuses primarily on the skilled artisan overcoming these limitations through routine optimization. Further, it is noted that Applicants arguments asserting that it would require routine experimentation are not specifically supported by any of the references of record, in particular as they pertain to providing predictable expression in the context of a transgenic

animal. Examiner would agree that promoter analysis in cells *in vitro* is common and routine, however even *in vitro* expression pattern of a regulatory sequence is not predictable and is subject to position of the transgene insertion into the genome, type of cell, nature of the promoter and other unknown factors affected by the conditions of the cell. More importantly, even when provided with a detailed expression pattern of the endogenous gene and a characterization of the 'isolated' promoter, the expression pattern would not simply extend to its use in a transgenic animal for providing the same expected expression pattern *in vivo*. The art recognizes that expression of a heterologous transgene in transgenic animals is subject to many variables without any clear expectation of successfully meeting the limitations set forth and encompassed by the instant claims. Moreover, because characterization and optimization of promoter activity *in vitro* does not simply extend the use of promoter sequences in transgenics *in vivo*, any optimization for use of specific sequences would have to be done *in vivo*. As noted in the previous office action, while Examiner would agree that the methodology for inserting a transgene into a the genome of an animal are becoming common, any methodology for optimizing promoters in this context is not routine. Further, given the unpredictability of transgene expression, even if sufficient materials and facilities could be provided to carry out the experiments for optimization, there is no simple expectation of success that a transgene in particular a promoter sequence out of the physical context of the endogenous gene would provide the same expression pattern as the endogenous gene. Examiner acknowledges that the specification has reduced to practice a large BAC genomic sequence and made modifications to said sequence, however there is no evidence that in the context of a transgenic animal that the sequences would meet the limitations for the required expression pattern set forth in the claims. The examples provided in the instant

specification fail to demonstrate that such methodology overcomes art recognized limitations for transgene expression. With respect to dependent claims reciting specific pathways (for example claim 17) and encompassing providing yet undefined genes in the context of specific disease states (claim 21), there is no evidence that art recognized limitation would not apply to these subsets of genes as well. It is also important to note that the specific diseases recited by the claims are complex and not all associated with any particular gene or gene expression. The amount of work in identifying, characterizing and establishing the correlation of a single gene to a particular disease is the subject of skilled artisans entire work. In addition to arguments provided above, the amount of experimentation to practice even the specific limitations set forth in dependent claims would be considered require more than experimentation. In this case, the identification of a specific genotype or phenotype cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

Enablement has been considered in view of the Wands factors (MPEP 2164.01(a)). In view of the quantity of experimentation required, the limited amount and general guidance presented, the absence of working examples supporting the claimed invention, the nature and breadth of the claimed invention, the state of the prior art and unpredictability of the art, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, for the reasons above and of record, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amendments to the claims and Applicants arguments have been fully considered, and have obviated the basis of each of the specific rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56 and 60 stand rejected under 35 U.S.C. 102(e) as being anticipated by Leinwand *et al.* (US Patent 6,353,151).

Applicants summarize the claims and specific embodiments required to be encompassed by the instant claims and argue that Leinwand *et al.* only teaches the use of regulatory sequences of a single gene of a heart specific promoter, and fails to disclose regulatory sequences from different characterizing genes. Applicants' arguments have been fully considered but not found persuasive.

Leinwand still anticipates the claims because the term 'a characterizing gene' is associated with (b) the regulatory sequences (see claim 1), not the general nature or name of the gene to be expressed. The genes used in Leinwand are two distinct and different genes from two different animals. The present claims include such a possibility, and only require that thegene was not present prior to the making of a transgenic animal. In addition, it would meet the limitation wherein the gene was not expressed before the animal was generated because any new sequence that is introduced could not have been expressed previously because it was not there. Examiner acknowledges that the promoter used by Leinwand *et al.* is a heart specific promoter, however they are obtained from two different genes from two different species of mammals. The claims broadly encompass any 'characterizing gene [that] is different" (claim 1). Clearly genes from two different species of mammals would be considered different.

Again, under the standards of 35 USC 102 a specific sequence from one mammal would not anticipate a second different sequence from another mammal. As set forth in the previous office action because Leinwand *et al.* provide methods for making transgenic mice and characterize the resulting transgenic demonstrating that they meet all the limitations set forth in the claims, it is maintained that the teachings of Leinwand *et al.* anticipate the instant claims.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v.*

Eagle Mfg. Co., 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-27 and 32-60 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-27 and 32-60 of copending Application No. 10/077,025.

Applicants acknowledge the basis of the rejection and request that the rejection be held in abeyance until the present claims have been found allowable.

Applicants request is noted however the rejection can not be held in abeyance. As noted in the previous office action, in the instant case the claims of each of the applications are duplicates of each other. No amendments to the claims in either application have been made to differentiate the instantly claimed inventions, therefore, the rejection is maintained.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach